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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/435,249	11/05/1999	JAY S. SCHNEIDER	SCH01.NP001	4962

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EXAMINER	
SCHMIDT, MARY M	

ART UNIT	PAPER NUMBER
1635	

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24

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/435,249	Applicant(s) SCHNEIDER, JAY S.	
	Examiner Mary M. Schmidt	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,9-12,30 and 34-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,9-12,30 and 34-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 November 1999* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☒ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet* .

Continuation of Attachment(s) 6). Other: See the PTO-892 filed with the Office action mailed 11/18/02.

DETAILED ACTION

1. The amendment filed 11/04/02, has been entered. The previously mailed Office action on 11/18/02 is superceeded by the new action below. Claims 1-4, 9-12, 30 and 34-37 are pending.

Claim Objections

2. Claim 37 is objected to because of the following informalities: the word "oligonucleotide" in line 1 should be plural. Appropriate correction is required.

Drawings

3. The drawings dated 11/05/99 have been approved by the official draftsman.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-4, 9-12, 30 and 34-37 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 1 is drawn to a method of treatment of Parkinson's disease in any mammal, comprising administering a therapeutically effective amount of antisense oligonucleotide comprising SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4 or SEQ ID NO:5 to the substantia nigra pars reticulata via a cannula for the down regulation of glutamic acid decarboxylase. Claim 2 specifies that the isoform of glutamic acid decarboxylase is GAD_{65}. Claim 3 specifies that the isoform of glutamic acid decarboxylase is GAD_{67}. Claim 4 specifies that the isoform of glutamic acid decarboxylase is a combination of GAD_{65} and GAD_{67}.

Claim 9 is drawn to a method of treatment of Parkinson's disease in any mammal, comprising administering a therapeutically effective amount of antisense oligonucleotide comprising SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4 or SEQ ID NO:5 to the internal globus pallidus via a cannula for the down regulation of glutamic acid decarboxylase. Claim 10 specifies that the isoform of glutamic acid decarboxylase is GAD_{65}. Claim 11 specifies that the isoform of glutamic acid decarboxylase is GAD_{67}. Claim 12 specifies that the isoform of glutamic acid decarboxylase is a combination of GAD_{65} and GAD_{67}.

Claim 30 is drawn to a method of down regulating glutamic acid decarboxylase in any mammal *in vivo*, comprising administering an antisense oligonucleotide directed to an initiation codon of glutamic acid decarboxylase mRNA to the substantia nigra pars reticulata or internal globus pallidus via a cannula, wherein said antisense oligonucleotide comprises SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4 or SEQ ID NO:5.

Claims 34-37 are drawn to methods of treating Parkinson's disease in a mammal, comprising administering a therapeutically effective amount of antisense oligonucleotides effective to inhibit translation of glutamic acid decarboxylase GAD_{65} and GAD_{67} mRNA to the substantia nigra pars reticulata or internal globus pallidus via a cannula for the down regulation of glutamic acid decarboxylase; wherein the antisense oligonucleotides are directed to the initiation codon of an glutamic acid decarboxylase mRNA; methods of down regulating glutamic acid decarboxylase in a mammal in vivo comprising administering antisense oligonucleotides effective to inhibit translation of glutamic acid decarboxylase GAD_{65} and GAD_{67} mRNA to the substantia nigra pars reticulata or internal globus pallidus via a cannula; wherein said antisense oligonucleotide are directed to the initiation codon of an glutamic acid decarboxylase mRNA.

The specification as filed teaches by way of example administration of antisense to GAD_{65} and GAD_{67} to rats or monkeys given unilateral lesions of the nigrostraiatal dopamine system using the neurotoxin 6-hydroxdopamine-hydrobromide (6-OHDA-HBr) to experimentally induce parkinsonism. Specifically via administration of instant SEQ ID NO:1 to the substantia nigra pars reticulata (5.3 mm behind bregma, 2.5mm lateral to the midline, 8.2 mm below the skull surface) in rats and via administration of instant SEQ ID NO:5 to dual cannulae overlying the internal segment of the globus pallidus bilaterally in squirrel monkeys. The specification as filed teaches on pages 8-10 that instant SEQ ID NOS. 1 and 2 are rat sequences, SEQ ID NO:1 to rat GAD_{67} and SEQ ID NO:2 to rat GAD_{65}, that instant SEQ ID NOS: 3 and 4 are human sequences, SEQ ID NO:3 to human GAD_{65} and SEQ ID NO:4 to human GAD_{67}, and the instant

SEQ ID NO:5 is a squirrel monkey sequence to monkey GAD_{67}. The specification teaches that these sequences are all directed to the initiation of translation region of the rat, human and monkey GAD_{65} and GAD_{67} gene sequences. The specification also states on page 9, line 15, that "[t]he results of this search indicated that the oligos were only homologous with the genes they were directed against." The specification further relates some of the homology among the different species and isoforms.

MPEP 2163 teaches the following conditions for the analysis of the claimed invention at the time the invention was made in view of the teachings of the specification and level of skill in the art at the time the invention was made:

> The claimed invention as a whole may not be adequately described where an invention is described solely in terms of a method of its making coupled with its function and there is no described or art-recognized correlation or relationship between the structure of the invention and its function. A biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence....A lack of written description issue also arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process....Generally, there is an inverse correlation between the level of skill and knowledge in the art and the specificity of disclosure necessary to satisfy the written description requirement....The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice..., reduction to drawings..., or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus.

The specification as filed has not adequately described a representative number of species of any antisense to GAD_{65} and/or GAD_{67} which have the *in vivo* functions claimed of treatment of Parkinson's in any mammal and/or down regulation/inhibition of the GAD isoforms in any mammal *in vivo*. There is a high level of unpredictability in the antisense art for design and use of antisense in mammals as shown in the 35 U.S.C. 112, scope of enablement rejection below. Although application has shown possession of instant SEQ ID NO:1 for the function in rat via administration to the substantia nigra pars reticulata via a cannula, and instant SEQ ID NO:5 for the function in monkey for down regulation of GAD via administration to the internal globus pallidus via a cannula, these results do not provide a nexus of the design and use of any other antisense to GAD in vivo because of the high level of unpredictability in the antisense art. Similarly, instant SEQ ID NOS. 2, 3 and 4, have not been shown to have a correlation to the breath of claimed functions *in vivo* because of the high level of unpredictability in the art for function of any antisense sequence *in vivo*. Since there is not a clear nexus provided by either the art or the specification as filed for the unpredictable factors such as administration of antisense to mammals in vivo for the claimed therapeutic and inhibitory effects of either or both of the GAD isoforms, one of skill in the art would not have recognized that application was in possession of the breath of claimed antisense to any GAD for the claimed functions *in vivo*.

6. Claims 1-4, 9-12, 30 and 34-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating Parkinson's disease in rat

comprising administration of the antisense of instant SEQ ID NO:1 via administration to the substantia nigra pars reticulata via a cannula, and methods of treating Parkinson's disease in monkey comprising administration of the antisense of instant SEQ ID NO:5 via administration to the internal globus pallidus via a cannula, does not reasonably provide enablement for administration of any of antisense to GAD as instantly claimed to any mammal for the treatment of Parkinson's disease nor specifically for the down regulation of either of the specific GAD isoforms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claim 1 is drawn to a method of treatment of Parkinson's disease in any mammal, comprising administering a therapeutically effective amount of antisense oligonucleotide comprising SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4 or SEQ ID NO:5 to the substantia nigra pars reticulata via a cannula for the down regulation of glutamic acid decarboxylase. Claim 2 specifies that the isoform of glutamic acid decarboxylase is GAD_{65}. Claim 3 specifies that the isoform of glutamic acid decarboxylase is GAD_{67}. Claim 4 specifies that the isoform of glutamic acid decarboxylase is a combination of GAD_{65} and GAD_{67}.

Claim 9 is drawn to a method of treatment of Parkinson's disease in any mammal, comprising administering a therapeutically effective amount of antisense oligonucleotide comprising SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4 or SEQ ID NO:5 to the internal globus pallidus via a cannula for the down regulation of glutamic acid decarboxylase.

Claim 10 specifies that the isoform of glutamic acid decarboxylase is GAD_{65}. Claim 11 specifies that the isoform of glutamic acid decarboxylase is GAD_{67}. Claim 12 specifies that the isoform of glutamic acid decarboxylase is a combination of GAD_{65} and GAD_{67}.

Claim 30 is drawn to a method of down regulating glutamic acid decarboxylase in any mammal *in vivo*, comprising administering an antisense oligonucleotide directed to an initiation codon of glutamic acid decarboxylase mRNA to the substantia nigra pars reticulata or internal globus pallidus via a cannula, wherein said antisense oligonucleotide comprises SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:4 or SEQ ID NO:5.

Claims 34-37 are drawn to methods of treating Parkinson's disease in a mammal, comprising administering a therapeutically effective amount of antisense oligonucleotides effective to inhibit translation of glutamic acid decarboxylase GAD_{65} and GAD_{67} mRNA to the substantia nigra pars reticulata or internal globus pallidus via a cannula for the down regulation of glutamic acid decarboxylase; wherein the antisense oligonucleotides are directed to the initiation codon of an glutamic acid decarboxylase mRNA; methods of down regulating glutamic acid decarboxylase in a mammal in vivo comprising administering antisense oligonucleotides effective to inhibit translation of glutamic acid decarboxylase GAD_{65} and GAD_{67} mRNA to the substantia nigra pars reticulata or internal globus pallidus via a cannula; wherein said antisense oligonucleotide are directed to the initiation codon of an glutamic acid decarboxylase mRNA.

The specification as filed teaches by way of example administration of antisense to GAD_{65} and GAD_{67} to rats or monkeys given unilateral lesions of the nigrostraiatal dopamine

system using the neurotoxin 6-hydroxdopamine-hydrobromide (6-OHDA-HBr) to experimentally induce parkinsonism. Specifically via administration of instant SEQ ID NO:1 to the substantia nigra pars reticulata (5.3 mm behind bregma, 2.5mm lateral to the midline, 8.2 mm below the skull surface) in rats and via administration of instant SEQ ID NO:5 to dual cannulae overlying the internal segment of the globus pallidus bilaterally in squirrel monkeys. The specification as filed teaches on pages 8-10 that instant SEQ ID NOS. 1 and 2 are rat sequences, SEQ ID NO:1 to rat GAD_{67} and SEQ ID NO:2 to rat GAD_{65}, that instant SEQ ID NOS: 3 and 4 are human sequences, SEQ ID NO:3 to human GAD_{65} and SEQ ID NO:4 to human GAD_{67}, and the instant SEQ ID NO:5 is a squirrel monkey sequence to monkey GAD_{67}. The specification teaches that these sequences are all directed to the initiation of translation region of the rat, human and monkey GAD_{65} and GAD_{67} gene sequences. The specification also states on page 9, line 15, that "[t]he results of this search indicated that the oligos were only homologous with the genes they were directed against." The specification further relates some of the homology among the different species and isoforms.

The specification as filed, however, does not provide how to make and use any of the recited SEQ ID NOS: 1-5 in any mammal for use as antisense in the methods of treatment or down regulation of either of the GAD isoforms as claimed. The specification as filed has not shown that the sequences of instant SEQ ID NOS: 2, 3 and 4 would be able to bind and inhibit GAD *in vivo* since none of the animal studies used these sequences, and a certain homology to instant SEQ ID NOS: 1 or 5 does not provide guidance as to an expectation of success to bind

and inhibit for the claimed functions *in vivo*. The specification as filed has only shown use of SEQ ID NO: 1 in rats to GAD_{67} and SEQ ID NO:5 in monkeys to GAD_{67}. The specification as filed has not shown any down regulation of GAD_{65} in any species, except prophetically. The results on pages 13-15 do not provide any data on the amount of down regulation of either of the GAD gene expression levels. In stead the results focus on the treatment effects such as a lessening of akinesia and bradykinesia in monkeys following administration of SEQ ID NO:5. Therefore, no guidance is provided as to guidance of down regulation of GAD_{65} in any species, nor down regulation of GAD_{67} in any species other than monkey and rat with instant SEQ ID NOS: 5 and 1, respectively.

There remains a high level of unpredictability in the art for design and use of the breath of claimed antisense to inhibit any GAD isoform in vivo via administration to any mammal for the claimed functions, either down regulation of a particular GAD isoform and/or the treatment of Parkinson's since the use of antisense *in vivo* is highly unpredictable as taught below:

There is a high level of unpredictability known in the antisense art for therapeutic, *in vivo* applications to mammals. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Note also Ma et al. who teach (on page 167) that "to gain therapeutic advantage using antisense-based technology, ODNs must have certain characteristics. They must be resistant to

degradation, internalize efficiently, hybridize in a sequence specific manner with the target nucleic acid, display adequate bioavailability with a favorable pharmacokinetic profile and be nontoxic." Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo*, the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Flanagan teaches, "oligonucleotides (*in vivo*) are not distributed and internalized equally among organs and tissues.... Unfortunantly, therapeutically important sites such as solid tumors contain very little oligonucleotide following intravenous injections in animals (page 51, column 2)." Ma et al. supports the difficulties of *in vivo* use of ODNs on pages 160-172. Jen et al. further taught that "given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive. While a number of phase I/II trials employing ONs have been reported..., virtually all have been characterized by a lack of toxicity but only modest clinical effects." (Page 315, col. 2) Green et al. summarizes that "the future of nucleic acid therapeutics using antisense ODNs ultimately depends on overcoming the problems of potency, stability, and toxicity; the complexity of these tasks should now be apparent. Improvements in delivery systems and chemical modifications may lead to safer and more efficacious antisense compounds with improved pharmacokinetics and reduced toxicities." (P. 103, col. B) Note also some of the major outstanding questions that remain in the art taught by Agrawal et al. On page 79, col. 2.

In vitro, antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Note also Ma et al. who teach that "*in vitro* subcellular distribution is dependent on the type of ODN modification, cellular system and experimental conditions. ODNs, once internalized, are distributed to a variety of subcellular compartments." (Page 168) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo*, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." Note Jen et al. who teach that "although mRNA targeting is impeccable in theory, many additional considerations must be taken into account in applying these strategies in living cells including mRNA site selection, drug delivery and intracellular localization of the antisense agent." (Abstract) Bennett et al. further taught that "although the antisense paradigm holds great promise, the field is still in its early stages, and there are a number of key questions that need to be answered and technical hurdles that must be overcome....The key issues concerning this class of chemicals center on whether these compounds have acceptable properties as drugs. These include pharmacokinetic, pharmacological and toxicological properties." (Page 13) As argued above, these issues remain unpredictable in the art for antisense oligonucleotide administration *in vivo*.

The McCarthy et al. reference (IDS filed June 3, 2002), page 217, section 4.3 "Aspects of antisense oligodeoxynucleotides in brain" further taught the unpredictability in the art for design and use of antisense to GAD_{65} and GAD_{67} in the brain. They teach that "[t]he use of antisense technology in behavioral neurobiology is emerging as a useful investigative tool but limitations of the method are also becoming increasingly apparent." Some of these problems they list are entrance of the antisense into the desired cell (uptake), toxicity, non-specific binding to other initiation start codon regions, and the unpredictability of non-specific effects depending on which route of administration is used: "In the current experiments some behavioral effects of the control oligo were observed. However, nonspecific effects of the control oligo were of a greater magnitude when delivered to the HYP versus the MCG, and not observed at all in the POA."

One of skill in the art would not accept on its face the successful delivery of the claimed breath of any antisense to any GAD isoform *in vivo* and further, treatment effects, in view of the lack of guidance in the specification and the unpredictability in the art. Neither the specification nor technology today teach general guidelines for successful delivery or treatment effects of antisense molecules in whole organisms. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo*, (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects for any such antisense oligonucleotide. While the specification as filed teaches the administration of instant SEQ ID NO:1 to rat and administration of instant SEQ ID NO:5 to monkey to specific brain

regions for a desired treatment effect, such evidence does not provide to one of skill in the art how to make any other antisense to any GAD isoform for administration to any mammal via administration to any brain region, for the claimed methods of down regulation of the GAD isoforms or treatment effects for Parkinson's. Each potential antisense must be considered on an antisense-by-antisense basis for its use *in vivo* in view of the high level of unpredictability in the antisense art for the unpredictable factors argued above. The specification as filed does not provide guidance therefore for the following claimed functions: down regulation or inhibition of any GAD_{65} in any mammal via administration of any potential and untested GAD_{65} antisense, or specifically instant SEQ ID NOS. 2 or 3; down regulation or inhibition of any GAD_{67} in any species of mammal via administration of any potential and untested GAD_{67} antisense, or specifically instant SEQ ID NO: 4; nor treatment of Parkinson's in any mammal via administration of any GAD isoform antisense via any route of administration other that those specifically taught in the specification in view of the unpredictability in the art for antisense and in view of the lack of specific guidance in the specification as filed for the unpredictable factors argued above for any such antisense to GAD. The lack of guidance in the specification as filed for these factors would therefore require "trial and error" experimentation beyond which is taught by the specification as filed. Therefore, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

7. Applicant's arguments filed Sept. 9, 2002, in response to the previous rejection of claims 23-29 and 31-33, have been fully considered but they are not persuasive.

Applicants state that "[t]he claims have been amended to more specifically recite the scope of the claims in an effort to more clearly set forth the invention as enabled. Amended claims 23 and 28 recite that the glutamic acid decarboxylase is GAD_{65} or GAD_{67} mRNA. One skilled in the art would be able to practice the claimed invention without being required to perform undue experimentation. Those skilled in the art could routinely produce, test and identify the various antisense oligonucleotides within the scope of the invention without undue experimentation. There is no reason to believe that one skilled in the art would be required to perform any amount of undue experimentation in order to make and use the claimed invention."

However, for the reasons argued above, the breath of the claims as amended remains unpredictable to make and use, and further, applicant has not shown possession of a representative number of species of antisense to GAD_{65} or GAD_{67} for the functions claimed.

8. The claims 1-4, 9-12, 30 and 34-37 are free of the prior art since the antisense oligonucleotide sequences of SEQ ID NOS:1-5 were not taught in the art at the time the invention was made nor were methods of treatment of Parkinson's disease via administration of these antisense or any antisense to GAD to the nigra pars reticulata via a cannula or internal

globus pallidus via a cannula were taught in the prior art prior to the instant invention. The McCarthy et al. reference cited in the IDS filed June 3, 2002, taught intracerebral administration of antisense to GAD_{65} and GAD_{67} to the POA (AP= -0.1 mm, depth= 8.o mm, lateral= 0.5 mm), HYP (AP= -3.1 mm, depth= 9.0 mm, lateral = 1.0 mm) and MCG (AP =-6.0 mm, depth= 4.5 mm, lateral = 0.5 mm) of female rats for the study of the antisense effects on reproductive behavior. The Mitsushima et al. reference cited in the IDS filed June 3, 2002, taught the administration of antisense to GAD_{65} and GAD_{67} to female rhesus monkeys to the stalk-median eminence. Neither of these references provides either motivation or expectation of success to administer antisense to GAD_{65} and GAD_{67} to rats or monkeys given unilateral lesions of the nigrostraiatal dopamine system using the neurotoxin 6-hydroxdopamine-hydrobromide (6-OHDA-HBr) (to experimentally induce parkinsonism) via administration of instant SEQ ID NO:1 to the substantia nigra pars reticulata (5.3 mm behind bregma, 2.5mm lateral to the midline, 8.2 mm below the skull surface) in rats nor via administration of instant SEQ ID NO:5 to dual cannulae overlying the internal segment of the globus pallidus bilaterally in squirrel monkeys for the treatment of Parkinson's.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *John LeGuyader*, may be reached at (703) 308-0447.

Any inquiry of a general nature or relating to the status of this application should be directed to *Katrina Turner*, whose telephone number is (703) 305-3413.

M. M. Schmidt
May 5, 2003

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600